REMARKS

Claims 1, 3-11 are pending and under consideration. Claims 1, 3, 6, 7, 9, 10 and 11 have been amended. Claim 8 has been cancelled without prejudice. Upon entry of the amendments, claims 1, 3-7, and 9-11 will be pending and under examination. The amendments are supported throughout the specification and entry is respectfully requested.

Regarding the Claim Objections

Applicants have amended claim 10 to correct the typographical error pointed out in the current Office Action. Accordingly, removal of the claim objection is respectfully requested.

Regarding 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 1 and 3- 11 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Applicants submit that, when viewed in light of the specification of which they are part, claims 1 and 3-11 are sufficiently clear and definite to the skilled person to comply with the second paragraph of section 112 of the Code.

Regarding the term "biological sample"

The claims are allegedly rendered indefinite by not reciting the source disease specific IgG. Applicants respectfully submit that this rejection has been rendered moot by the amendment to claim 1, which replaces the term "biological sample" with "orbital or skin sample" to clarify the source of the disease specific IgG.

Regarding the source of the T-cells

As an additional basis for rejection the Office asserts that, while claims 3-6 require T cells to perform the methods, the source of the T cells is allegedly unclear. Applicants respectfully disagree.

The Court of Appeals for the Federal Circuit has held and repeatedly affirmed that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content

of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See, e.g., In *re Marosi*, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983); *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 U.S.P.Q. 1 (Fed. Cir. 1984); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983); and *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 U.S.P.Q.2d 1225 (Fed. Cir. 1999) (district court failed to consider the knowledge of one skilled in the art when interpreting the patent disclosure).

The specification describes the general migration assay to the skilled person and further provides a citation to a Journal of Immunology article for complete detail. US 2003/0096317, [0076]. Briefly, fibroblasts from TAO and normal orbital tissues were seeded and grown, followed by addition of normal or TAO IgGs. *Id.* Chemotaxis was subsequently examined using Boyden chambers to which T lymphocytes were added. *Id.* In view of *thes*e teachings, it is respectfully submitted that the claims, when properly analyzed in light of the application disclosure, the teachings of the prior art, and the claim interpretation that would be given by the skilled person at the time of the invention, are sufficiently clear to meet the requirements of 35 U.S.C. 112, 2nd paragraph. Accordingly, Applicants respectfully request removal of this basis for rejecting claims 3-6 as allegedly unclear.

Regarding 35 U.S.C. § 112, First Paragraph (Enablement)

Applicants respectfully traverse the rejection of claims 1 and 3-11 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Essentially, the Office argues that the claims are enabling for a method of detecting Graves' disease in a human patient that encompasses obtaining a orbital or skin sample and for specific chemical markers. While Applicant respectfully maintain that the specification enables the full scope of the claimed invention, the claims have been amended to recite the embodiments indicated in the Office Action to be enabled, rendering moot the rejection. Accordingly, Applicants respectfully request removal of the rejection of claims 1 and 3-11 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Regarding 35 U.S.C. § 112, First Paragraph (Written Description)

Applicants respectfully traverse the rejection under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention of claims 1 and 3-11.

Essentially, the Office argues that the claims are sufficiently described for a method of detecting Graves' disease in a human patient that encompasses obtaining a orbital or skin sample and for specific chemical markers. While Applicant respectfully maintain that the specification provides written description for the claimed invention, the claims have been amended to recite the embodiments indicated in the Office Action to be sufficiently disclosed, rendering moot the rejection. Accordingly, Applicants respectfully request removal of the rejection under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention of claims 1 and 3-11.

Regarding 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 1-3 and 7-8 under 35 U.S.C. § 102(a) as allegedly being anticipated by Kendall-Taylor et al., Journal of Endicronology (1990).

Kendall-Taylor, in a brief abstract, discuss a possible modulatory role of TAO IgG's on IGF-1 levels associated with extraocular myoblasts. Kendall-Taylor et al. do not teach or suggest the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R). The IGF-1 receptor is not mentioned, directly or indirectly, in the short abstract.

Claimed subject matter is "anticipated" when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. *See Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003); *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1267-69 (Fed. Cir. 1991). An anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation. *See Amgen Inc. v.*

Hoechst Marion Roussel, Inc., 457 F.3d 1293, 1306-07 (Fed. Cir. 2006); *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. and Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003).

To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting Connell v. Sears, Roebuck and Co., 722 F.2d 1542, 1548 (Fed. Cir. 1983)); see *also, e.g., In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) ("[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference" (emphasis in original)).

Because Kendall-Taylor et al. do not teach or suggest the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R). The IGF-1 receptor is not mentioned, directly or indirectly, and no suggestion of a relationship between binding of TAO IgGs to the IGF-1R is found in the Kendall-Taylor abstract. Accordingly, Applicants respectfully request removal of the rejection of claims 1, 3 and 7-8 under 35 U.S.C. § 102(a) as allegedly being anticipated by Kendall-Taylor et al., Journal of Endicronology (1990).

Applicants respectfully traverse the rejection of claims 1, 3 and 7-8 are rejected under 35 C. 102(b) as being anticipated by Weightman et al., Journal of Endicronology (1993).

Weightmann et al. discusses the presence of antibodies to the IGF-1R in the sera of patients with Graves' disease and speculates that the antibody binding to the IGF-1R may have biologically significant effects, by activating the IGF-I receptor. Weightman does not teach or suggest determining fibroblast activation by measuring the level of a chemical marker expressed by said IgG-activated fibroblasts or by measuring T cell migration towards said fibroblasts in said orbital or skin sample. In addition to not disclosing all elements of the rejected claims, the Weightman et al. abstract is not enabling. In order to anticipate a claimed invention, a prior art reference must enable one of ordinary skill in the art to make the invention without undue experimentation. *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008) (citing *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1379 (Fed. Cir. 2007)). Accordingly, Applicants respectfully request removal of the rejection of claims 1, 3 and 7-8 under 35 U.S.C. § 102(a) as allegedly being anticipated by Weightman et al., Journal of Endicronology (1993).

Applicants respectfully traverse the rejection of claims 1, 3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Rotella et al., *J. Clin. Endocrinol. Metabol.* (1986) 62:357-367.

Rotella et al. describes an assay for measuring the activity of autoantibodies active in causing ophthalmopathy and concludes that some but not all *TSH receptor* monoclonal antibodies have been found to duplicate the action of the autoimmune IgGs from the ophthalmopathy patients. Accordingly, Applicants respectfully request removal of the rejection of claims 1, 3 and 7-8 under 35 U.S.C. § 102(a) as allegedly being anticipated by Rotella et al.

Applicants respectfully traverse the rejection of claims 1, 3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Perros et al., *Balliere's Clinical Endocrinology and Metabolis*m, 9(1):115-135 (1995).

Perros et al. discuss a possible role of IGF-1R as an autoantigen in TAO. Kendall-Taylor et al. do not teach or suggest the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R). Accordingly, Applicants respectfully request removal of the rejection of claims 1, 3 and 7-8 under 35 U.S.C. § 102(a) as allegedly being anticipated by Perros et al.

Regarding 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1 and 3-11 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kendall-Taylor et al.; Weightmann et al.; Perros et al.; or Rotella et al. each in view of Sciaky et al. and Urn et al.

Neither Sciaky et al. nor Urn et al. cure the deficiencies of the primary references discussed above. In particular, the combination of Kendall-Taylor et al.; Weightmann et al.; Perros et al.; or Rotella et al. each in view of Sciaky et al. and Urn et al., does not teach or suggest the method of detecting Graves' disease in a patient by obtaining an orbital or skin sample including fibroblasts from the patient, and detecting the activation of fibroblasts by binding of disease specific IgG to the IGF-1 receptor (IGF-1R) relative to a control wherein an increased presence of IgG-activated fibroblasts compared to the control indicates Graves' disease, and wherein fibroblast activation is determined by measuring the level of a chemical marker expressed by the IgG-activated fibroblasts or by measuring T cell migration towards the

fibroblasts in the orbital or skin sample. Each of the primary references: Kendall-Taylor et al.; Weightmann et al.; Perros et al.; and Rotella has particular deficiencies as disclosed above. Sciaky et al. and Urn et al. do not address any of the deficiencies of the primary references.

As previously held by the Federal Circuit and reiterated by the KSR Court, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated **reasoning** with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) (emphasis added). The U.S. Patent and Trademark Office recently promulgated guidelines for Examiners in making obviousness determinations in view of the U.S. Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.* Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., 72 Fed. Reg. 57,526 (2007) ("Guidelines") One important feature of the Guidelines is an *explicit requirement* that an Examiner provide articulated reasons for the factual determinations underlying an asserted *prima facie* case of obviousness. This focus is consistent with the rule set down in the KSR decision that a factfinder must provide "reasons" why an invention would have been obvious to one of ordinary skill in the art. ." *KSR* at 1741. In explicating this aspect of the Supreme Court's decision, the Guidelines set forth explicit factual findings that an Examiner must articulate to support an obviousness rejection. For an obviousness rejection based on a rationale of combining references, the Examiner *is required to articulate* the following: (1) a finding that the prior art included *each element claimed*; (2) that one of ordinary skill in the art could have combined the elements by known methods, and that in combination each element merely would function as it did separately; (3) one of ordinary skill in the art would have recognized that the results of the combination were predictable; and (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. Fed. Reg. at page 57,529. In the current Office Action, the Examiner lumps together four primary references that are *each* alleged to render obvious the claimed invention in combination with the cited secondary references. This amounts to four separate obviousness rejections supported by primary references with very different teachings. The Examiner has not articulated a reasoned obviousness rejection as required by the Guidelines tailored to each reference. In addition to this procedural deficiency in the rejection, the substantive deficiency is that neither Sciaky et al. nor Urn et al. cure the deficiencies of the primary references discussed above. In particular, the combination of Kendall-Taylor et al.;

Weightmann et al.; Perros et al.; or Rotella et al. each in view of Sciaky et al. and Urn et al., does not teach or suggest the claimed methods.

Accordingly, Applicants respectfully request removal of the rejection of claims 1 and 3-11 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kendall-Taylor et al.; Weightmann et al.; Perros et al.; or Rotella et al. each in view of Sciaky et al. and Urn et al.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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